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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/677,093	09/30/2003	John Rudolph Desjarlais	33604/US/2 463077-246	4088

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EXAMINER
SHAFER, SHULAMITH H

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 07/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

Office Action Summary	**Application No.** 10/677,093	**Applicant(s)** DESJARLAIS ET AL.	
	Examiner Shulamith H. Shafer, Ph.D.	**Art Unit** 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *6,7,9 and 12-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8,11 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/17/04*.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, And/Or Claims

Applicant's election, without traverse, of the Group I, claims 1-12 and 19, drawn to an interferon and election, without traverse of IFN-beta, as the elected species on 17 February 2006 in response to the 13 January 2006 office action is acknowledged. Applicants election, without traverse, of SEQ ID NO:35, in response filed of 17 April 2006 in response to further requirement of species election (Office Action of 13 March 2006) of specific sequence is acknowledged. In summary, applicants have elected Group I, claims 1-12, and 19, drawn to IFN-beta of SEQ ID NO:35 as the elected invention and species. Claims 1-19 are pending in the instant application. Claims 6, 7, 9, 12-18 are withdrawn as being drawn to a non-elected invention. Claims 1-5, 8, 11 and 19 are under consideration to the extent they read on the elected invention.

Objections

Claims 3 and 5 are objected to as encompassing non-elected inventions. Appropriate correction is required.

Rejections

35 U.S.C. § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5, 8, 11, and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, the independent claim of the instant invention, is indefinite in reciting "at least one modulated characteristic as compared to the naturally occurring interferon". It is unclear which characteristic is to be modulated and how this characteristic is modulated. The term can be read to mean changes in structural or functional characteristics; reading the term thusly, any circular permutein would meet the claim limitation.

Claims 2-5, 8, 11 and 19 are included in this rejection as depending from a rejected claim.

35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5, 8, 11, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pastan et al. (2000, US 6,011,002) in view of Radhakrishnan et al. (1999, J Mol. Biol. 286:151-162). The claims of the instant invention are drawn to a type I interferon-beta of SEQ ID NO:35, wherein the interferon-beta is circularly permuted. Claim 1, the independent claim of the instant invention recites the limitation that the circularly permuted or cyclized molecule "has at least one modulated characteristic as compared to the naturally occurring interferon". By definition, all circular permuteins would be expected to have different characteristics than the wild-type molecule, as all circular permuteins have sequences that differ from the wild-type molecule.

Pastan et al teach modified forms of molecules which are "circularly permuted" in which the termini have been joined together, either directly or through a linker to produce a circular molecule, and then the circular molecule is opened at another location to produce a new linear molecule with termini different from the termini in the original molecule (Column 4, lines 37-42). Pastan et al. teach that the native ligand, growth factor, or protein provides a reference point for the ligand, growth factor or protein prior to rearrangement into a circularly permuted molecule (Column 5, lines 15-18). The reference discloses that the term "ligand" encompasses cytokines (Column 5, lines 39-44). The person of ordinary skill in the art would recognize that interferons are cytokines. The process of circular permutation is schematically illustrated in Fig. 1 of the '002 patent. The reference teaches "there are two requirements for the creation of an active circularly permuted protein: 1) The termini in the native protein must be favorably located so that creation of a linkage does not destroy biological activity; and 2) There must exist an "opening site" where new termini can be formed without disrupting a region critical for protein folding and desired biological activity" (Column 8, lines 38-44). The reference teaches that good candidates for circular permutation are proteins in which the termini of the original protein are in close proximity and that in roughly one third of the known structures of globular proteins the termini are in relatively close proximitiy (Column 8, lines 45-53). Pastan et al. teach that the selection of an opening site may be determined by a number of factors: Where the three dimensional conformation of the protein is known or predicted, preferred opening sites will be located in regions that do not show a highly regular three-dimensional structure. It is preferred that opening sites be selected in regions of the protein that do not show secondary structures such as alpha helices, pleated sheets and the like (Column 9, lines 36-43). Where substitution of certain amino acids, or modification of said amino acids does not modify the activity of the protein, it is expected that the modified amino acids are not critical to the protein's activity and are potentially good candidates for opening sites (Column 9, lines 54-60). Where the protein is a member of a family of related proteins, one may infer that the highly conserved sequences are critical for biological activity, while the variable regions are not. Preferred opening sites are then selected in regions of the protein that do not show highly conserved sequence identity between various members of the protein family (Column 10, lines 1-6). Pastan et al. teach that the circularly permuted protein may possess specificity and binding affinity greater than the native ligand (Column 7, lines 15-18). The reference teaches that additional modifications may be made to the circularly permuted ligand (Column 17, lines 38-40). Additonally, Pastan et al. teach that the circularly permuted ligands can be components of pharmaceutical compositions (Column 21, lines 37-42).

Pastan et al. do not specifically teach a circularly permuted molecule wherein the molecule is an interferon molecule or specifically a molecule of SEQ ID NO:35.

Radhakrishnan et al. teach that the termini of human IFN-β molecule and mouse IFN-β molecule are in close proximity (Figure 5). The reference teaches that these molecules have a common conserved structural core which consists of helix A (residues 8-21) AB2 loop (residues 34-39), helix B (residues 53-68), helix C (residues 79-100) and helices D and E (residues 117-155) (page 155, column 2, 1st paragraph).

It would been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to utilize the detailed teachings of Pastan et al. instructing the skilled artisan how to make a circular permuted cytokine (an interferon molecule being considered a cytokine) including how to choose an opening site, and the teachings of Radhakrishnan et al. to make a circular permuted interferon molecule with a breakpoint or opening site between any of amino acid residues 22-33, 40-52, 69-78, or 101-116, since these are the portions of the amino acid sequence of the interferon-beta molecule that do not encompass highly regular three-dimensional structure such as alpha helices, pleated sheets and the like. Thus, the skilled artisan would be directed to make a molecule of SEQ ID NO:35, wherein the breakpoint or opening site is located between residues 27 and 28. One would be motivated to do so because the Pastan et al. teach that circularly permuted ligands are as fully active as the original ligands, may possess specificity and binding affinity greater than the native ligand, and are especially useful when applied as a component in a chimeric molecule such as a fusion protein (Column 2, lines 19-21). One would have expected success because the methods of making circularly permuted molecules are taught by the Pastan et al.

Conclusions

No claims are allowed.

Lorraine Spector

LORRAINE SPECTOR
PRIMARY EXAMINER

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shulamith H. Shafer, Ph.D. whose telephone number is 571-272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SHS